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(54) Title: GRF ANALOG COMPOSITION AND THEIR USE

(57) Abstract: The present invention relates to compositions for improving daytime vigilance and/or cognitive function, for improving a metabolic condition, for improving anabolism in a catabolic condition and for improving and/or reconstituting immune function in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

GRF ANALOG COMPOSITIONS AND THEIR USE

BACKGROUND OF THE INVENTION

(a) Field of the Invention

[0001] This invention relates to the new uses of GRF and analogs thereof (1) for stimulating day-time vigilance and/or cognitive functions in conditions related to aging or mild cognitive impairment, (2) for improving metabolic conditions associated with fat accumulation and/or hypercholesterolemia, the metabolic conditions being such as obesity, HIV-related lipodystrophy, metabolic syndrome or syndrome X, (3) for improving anabolism in catabolic/wasting conditions such as those observed in Chronic Renal Failure, congestive heart failure AIDS, following hip fracture, trauma, or major surgery, particularly in elderly subjects, and (4) for improving immune function or reconstitution in immune deficiency states such as aging, HIV or following high-dose chemotherapy and/or radiotherapy.

(b) Description of Prior Art

Cognitive functions

[0002] Cognitive abilities are impaired in a number of certain conditions including advancing age. Deleterious changes observed with aging affect particularly fluid intelligence, or abilities involving concept formation, rule discovery, planning behavior, and non-verbal reasoning. Conversely, crystallized intelligence, or abilities dependent upon accumulated experience and education is relatively resistant to age-related decline. It has been suggested that the decline in GH and IGF-1 observed with aging contribute to the impaired cognitive function.

[0003] There is large evidence from both animal and human studies that administration of GRF, GH or IGF-1 has significant effect on cognitive functions in conditions where these functions are impaired. For example, this has been demonstrated with GH therapy in GH-deficient adults (Deijen JB, *et al.*, *Psychoneuroendocrinology* 1998 **23(1)**:45-55), and with administration of IGF-1 or GRF in the healthy elderly (Aleman A *et al.*, *J*

Clin Endocrinol Metab 1999 **84(2)**:471-475; Vitiello M.V., *et al.*, *Gerontologist* 2002 **40**(Special Issue 1):39).

Immune Function

[0004] Aging is accompanied by diminished circulating GH and IGF-1 levels observed in parallel with a declined function of the immune system, particularly affecting the T-cell mediated immunity. The age-related T-cell immune deficiency has been partly attributed to a progressive atrophy of the thymus gland and is considered to be causally related to the increased risk and severity of acquired infections observed in the elderly.

[0005] GH and IGF-1 are known to play an integrating role in the development and function of the immune system, as endocrine and/or autocrine/paracrine factors, and their administration has been shown to reverse age-related immune changes. Immune enhancing effects of these factors have been investigated in other immune deficiency states and encouraging results have been observed in HIV-positive patients (Napolitano LA, *et al.*, *AIDS* 2002 **16(8)**:1103-1111) and in animal models of radiotherapy preceding bone marrow transplantation (Sun R, *et al.*, *BMT Meetings*, Feb 22-26 Orlando, FL, **Abstract 27** 2002:68-69).

Catabolism or Muscle Wasting

[0006] Muscle protein catabolism, or muscle wasting, accompanies many diseases including all critical illness, regardless of the primary cause of disease. It is an important factor for the long-term prognosis and the length of hospital stay and recovery, and may also be a limiting factor for survival. Although many therapeutic tools have been investigated including specific nutritional treatment, there is still a strong need for more effective strategies to counteract protein catabolism.

[0007] Previous studies have reported that GH treatment increases muscle mass in older patients. The anabolic effects and abilities of GH to reverse or attenuate muscle wasting have been investigated in several patient groups. GH has been shown to improve nitrogen balance, an index of net whole-body protein balance, after major gastro-intestinal surgery, burn injury, or major trauma. Anabolic effects have been translated into clinical benefits in COPD patients (improvement of the maximal inspiratory

pressure) (Papte GS, *et al.*, *Chest* 1991 **99(6)**:1495-1500) and elderly patients undergoing surgery following hip fracture (improvement of functional recovery defined as return to independence) (Van der Lely AJ, *et al.*, *Eur J Endocrinol* 2000 **143(5)**:585-592). Finally, rGH has been recently approved for the management of AIDS-wasting based on results showing increased body weight, lean body mass and functional performance following 12 weeks of treatment (Schambelan M, *et al.*, *Ann Intern Med* 1996 **125(11)**:873-882).

Syndromes associated with fat accumulation

[0008] Fat accumulation is observed in a range of conditions or syndromes such as obesity, metabolic syndrome, and the recently described HIV-related lipodystrophy syndrome. All these conditions include features that are known to increase the risk of diabetes and/or cardiovascular diseases.

[0009] The metabolic syndrome, also known as syndrome X, affect persons with frank obesity as well as those with an increased amount of abdominal fat, and is characterized by insulin resistance, dyslipidemia (hypertriglyceridemia, low serum HDL cholesterol levels, and increased LDL cholesterol levels) and hypertension.

[0010] Initially described in 1998, the HIV-related lipodystrophy syndrome is now known to occur in a significant proportion of HIV positive patients receiving protease inhibitor (PI) or non-PI –containing highly active antiretroviral therapy (HAART) regimens. This syndrome includes areas of fat gain (in the abdomen primarly as visceral, breast and/or dorsocervical regions) and/or areas of subcutaneous fat loss (especially in the facial fat pads, limbs and buttocks) that are accompagnied, as in the syndrome X, by metabolic abnormabilites, mainly insulin resistance and hyperlipidemia.

[0011] Growth Hormone is known for its lipolytic properties, and its potential role in reversing several of the body fat and associated metabolic abnormalities has been actively studied. Beneficial effects have been shown in GH-deficients individuals (Gotherstrom G. *et al.*, *J Clin Endocrinol Metab* 2001 **86(10)**:4657-4665), non-HIV patients with abdominal obesity (Johannsson G, *et al.*, *J Clin Endocrinol Metab* 1997,

82(3):727-734) as well as HIV positive patients experiencing lipodystrophy (Engelson ES, *et al.*, *J Acquir Immune Defic Syndr* 2002 **30(4)**:379-391).

SUMMARY OF THE INVENTION

[0012] In accordance with the present invention, there is provided a composition improving daytime vigilance and/or cognitive function in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

[0013] The composition in accordance with a preferred embodiment of the present invention, wherein the cognitive function is selected from the group consisting of thinking, reasoning, problem solving and memory.

[0014] In accordance with the present invention, there is provided the use of an effective amount of the composition of the present invention for improving daytime vigilance and/or cognitive function in a subject.

[0015] In accordance with the present invention, there is provided a composition for improving a metabolic condition in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

[0016] The composition in accordance with a preferred embodiment of the present invention, wherein the metabolic condition is associated with fat accumulation and/or hypercholesterolemia, preferably obesity, HIV-related lipodystrophy, metabolic syndrome and syndrome X.

[0017] In accordance with the present invention, there is provided a composition for improving anabolism in a catabolic condition in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

[0018] The composition in accordance with a preferred embodiment of the present invention, wherein the catabolic condition is related to one selected from the group consisting of chronic renal failure, AIDS, hip fracture, trauma or major surgery in a subject.

[0019] In accordance with the present invention, there is provided the use of an effective amount of the composition of the present invention for improving anabolism in a catabolic condition in a subject.

[0020] In accordance with the present invention, there is provided a composition for improving and/or reconstituting immune function in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

[0021] In a preferred embodiment of the present invention, the composition of the present invention is for a subject in an immune deficiency state, preferably caused by one selected from the group consisting of aging, HIV infection, chemotherapy treatment and radiotherapy treatment.

[0022] In a preferred embodiment of the present invention, the composition is comprising a GRF compound of the formula

X ——GRF Peptide (A)

wherein;

the GRF peptide is a peptide of formula B;

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-Arg-A30-R0 (B) (SEQ ID NO:1)

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

A28 is Ser or Asn;

A30 is a bond or any amino acid sequence of 1 up to 15 residues;

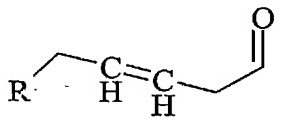
R0 is NH_2 or NH-(CH_2)n-$CONH_2$, with n=1 to 12 and;

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and the hydrophobic tail defining a backbone of 5 to 7 atoms;

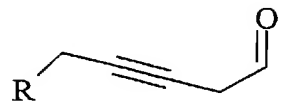
wherein the backbone can be substituted by C1-6 alkyl, C3-6 cycloalkyl, or C6-12 aryl and the backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

the moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C3-9 cycloalkyl, and C6-12 aryl.

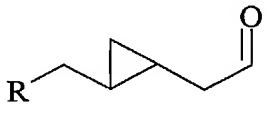
[0023] In a preferred embodiment of the present invention, the composition of the present invention is having X selected from the group consisting of:



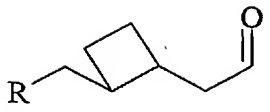
1 (R=H or CH_3 or CH_2CH_3)
cis or *trans*



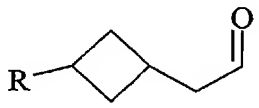
2 (R=H or CH_3 or CH_2CH_3)



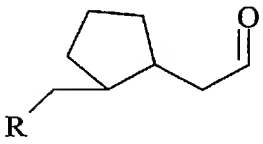
3 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



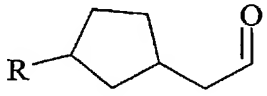
4 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



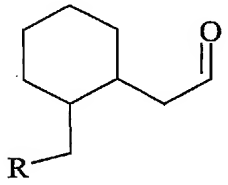
5 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



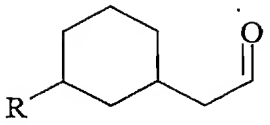
6 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



7 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



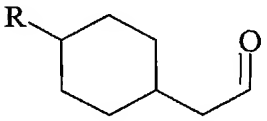
8 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



9 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R ≠ H)

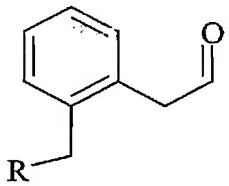
both as racemic mixtures
or pure enantiomeric pairs



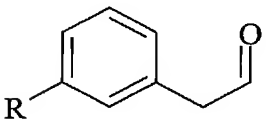
10 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R ≠ H)

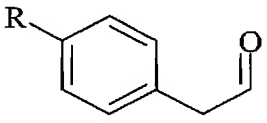
both as racemic mixtures
or pure enantiomeric pairs



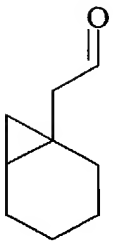
11 (R=H or CH_3 or CH_2CH_3)



12 (R=H or CH_3 or CH_2CH_3)



13 (R=H or CH_3 or CH_2CH_3)



14

[0024] In a more preferred embodiment of the present invention, the GRF analog is (hexenoyl trans-3) hGRF(1-44)NH2.

[0025] The composition of the present invention is preferably administered in an amount of about 0,0001 to 1 mg/kg per day to said subject, preferably through a route selected from the group consisting of oral, transdermal, intravenous, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical route.

[0026] For the purpose of the present invention the following terms are defined below.

[0027] The term "analog" is intended to mean a molecule of different structure but having a biological function similar to the structures of the GRF or to a biologically functional fragment thereof which may include peptidomimetics. Peptidomimetics may be conveniently prepared by direct chemical synthesis using methods well known in the art.

[0028] The term "subject" is intended to mean any mammal including, but not limited to, human, canine, feline, equine, caprine, bovine, porcine and ovine.

[0029] The term "cognitive function" is intended to mean functions including, but not limited to thinking, reasoning, memory and problem solving.

[0030] The term "catabolic/wasting conditions" is intended to mean condition including, but not limited to, frail bones, low muscular mass and muscle wasting.

[0031] In the present application, the compound identified as TH9507 is the [hexenoyl-trans-3-Tyr1]hGRF(1-44)NH_2.

[0032] All references herein are hereby incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] Fig. 1 illustrates the differences between treatment groups in changes from baseline to week 2 in the mean reaction time of the Continuous Performance Test (CPT);

[0034] Fig. 2 illustrates changes from baseline to day 9 in Pz amplitude of evoked related potential (P300) during wakefulness;

[0035] Fig. 3 illustrates mean AUC of antigen-specific proliferative T cell response;

[0036] Fig. 4 illustrates the percentage of subjects with protective antibody titers (>1/40) for B/Victoria; and

[0037] Fig. 5 illustrates the variation of mean IGF-1 levels during time with placebo, 2mg/day TH9507, 0.5 mg/day TH9507 and 1mg/day TH9507.

DETAILED DESCRIPTION OF THE INVENTION

[0038] In accordance with the present invention, there is provided new uses for GRF analogs.

[0039] GRF analogs are suitable for the purpose of the present invention.

[0040] More particularly suited are those hydrophobic GRF analogs of formula A:

X ——GRF Peptide (A)

wherein;

the GRF peptide is a peptide of formula B;

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-Arg-A30-R0 (B)

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

A27 is Met, Ile or Nle;

A28 is Ser or Asn;

A30 is a bond or any amino acid sequence of 1 up to 15 residues;

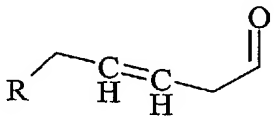
R0 is NH_2 or NH-(CH_2)n-$CONH_2$, with n=1 to 12 and;

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and said hydrophobic tail defining a backbone of 5 to 7 atoms;

wherein said backbone can be substituted by C1-6 alkyl, C3-6 cycloalkyl, or C6-12 aryl and said backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

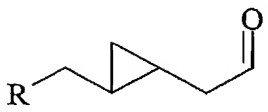
said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C3-9 cycloalkyl, and C6-12 aryl.

[0041] According to a preferred embodiment of the present invention, X is selected from the group consisting of:

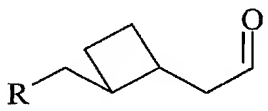


1 (R=H or CH_3 or CH_2CH_3)
cis or *trans*

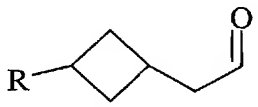
2 (R=H or CH_3 or CH_2CH_3)



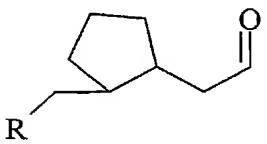
3 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



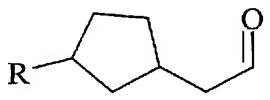
4 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



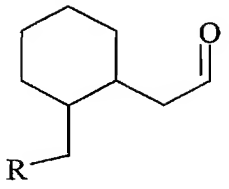
5 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



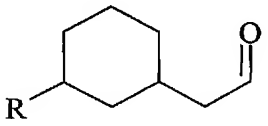
6 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



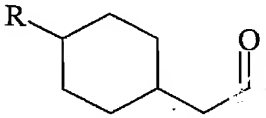
7 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



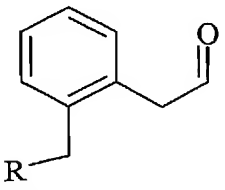
8 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



9 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



10 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



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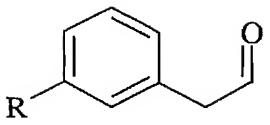
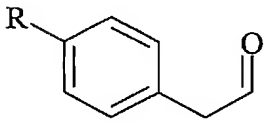
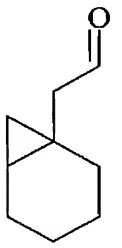


12 (R=H or CH_3 or CH_2CH_3)



13 (R=H or CH_3 or CH_2CH_3)



14

are of particular interest.

Example 1

Administration of TH9507 for improving daytime vigilance in subjects with sleep maintenance insomnia

[0042] The present example shows the effect of a 14 day-administration of 2 doses of TH9507 (0.1 mg and 1 mg) on vigilance parameters in subjects of 35 to 50 years of age exhibiting sleep maintenance insomnia.

Material and Methods

[0043] The study involved 82 patients exhibiting sleep maintenance insomnia (20 females, 62 males; mean age 43.2 ± 5.4 years). Patients were selected based on the Pittsburgh Sleep Quality Index (Score ≥ 5), the Walters Criteria for Sleep Maintenance Insomnia, and the Beck Questionnaire (Score ≤17). The primary exclusion criteria were other primary sleep disorders and the use of any products affecting sleep or vigilance in the 30 days prior to entering the study.

[0044] The study was a randomized, double-blind, placebo-controlled, parallel group and multicenter evaluation of two doses of TH9507 (0.1 mg and 1 mg) administered daily by subcutaneous injection at bedtime for 14 consecutive days. To evaluate vigilance and performance in the morning, patients underwent a battery of cognitive tests including the Continuous Performance Test (CPT) at Baseline and at the end of the treatment period.

[0045] The CPT has been described in the literature as a measure of consistency in responding and ability to sustain attention over time (Aleman A, *et al.*, *J Clin Endocrinol Metab* 1999 **84**(2):471-475). This test required subjects to press space bar each time letter "A" was followed by "X". Omission and commission errors, and Mean Reaction Time of correct responses were analyzed.

Results

[0046] Demographic characteristics by treatment group are displayed in the following table :

Table 1
Demographic (screening) data by treatment groups

	Placebo N=29	0,1 mg N=26	1 mg N=27	p value
Age (Mean ± SD) (Range)	44.0 ±5.8 (35-56)	43.2 ±5.8 (34-60)	42.3 ± 4.5 (34-50)	0.53 (F-test)
Gender Males Females	21 8	19 7	22 5	0.68 (chi-square test)
Weight (kg) (Mean ± SD)	78.0 ± 14.3	78.2 ± 12.4	79.3 ± 15.3	0.94 (F-test)

[0047] As illustrated in Fig. 1, the Mean Reaction Time of the CPT was significantly and markedly decreased in the 0.1 mg group when compared to placebo. The decrease from baseline to Day 9 was of 45.85 ms (P=0.023 when compared to placebo as analyzed by an ANOVA model). No significant effect was observed in the 1 mg group. Circulating IGF-1 and IGFBP-3 levels were significantly increased at week 2 in the 1 mg

group when compared to placebo (P<0.0001, ANOVA on changes from baseline). As expected, the 0.1 mg did not affect these parameters (P=0.07 and P=0.99 for IGF-1 and IGF-BP3 respectively, ANOVA model on changes from baseline).

[0048] Additional data on effects of TH9507 on vigilance obtained in a previous study are presented in Fig. 2. In this study, TH9507 was administered daily for 7 days in a cross-over design. This study involved 12 healthy subjects aged between 50 to 65 years, exhibiting age-related sleep impairment (Pittsburgh Sleep Quality Index Score from 3 to 7). At the end of the treatment period, daytime vigilance was significantly enhanced when compared to placebo in subjects receiving 1 mg of TH9507, as assessed by P300, an event-related potential test. Changes from Baseline to day 9 in the Pz amplitude of the Evoked Related Potential (P300) observed in the placebo and 1 mg group were as follows : Placebo, -15%; 1 mg, +55%, P=0.0114, as analyzed by an ANOVA model.

[0049] In both studies, the safety profile of TH9507 was comparable to that of the placebo, except for a higher incidence of reactions at the site of injection observed at 1 mg in the insomnia study.

[0050] In summary, these results provide evidence that TH9507 improves daytime vigilance in sleep maintenance insomnia subjects and would favor a direct mechanism of action of TH9507, not mediated by IGF-1. Data are supported by those obtained by Vitiello et al (Vitiello M.V., *et al.*, *Gerontologist* 2002 **40**(Special Issue 1):39-N/A. using hGRF in cognitive tests involving psychomotor and perceptual processing speed (Deijin JB *et al*, *Psychoneuroendocrinology* 1998 **23**(1):45-55) and may support further clinical investigations in subjects with impaired cognitive functions.

Example 2

Effects of TH9507 on the immune response to influenza vaccination in elderly subjects

[0051] The present example describes immune findings following an influenza vaccination challenge in elderly subjects.

Material and Methods

[0052] Eighty seven (87) subjects aged 75 years in average were included in a double-blind, randomized, placebo-controlled study. TH9507 or a placebo was administered at a daily dose of 1 or 2 mg by subcutaneous injection for 8 weeks. Follow-up assessments were conducted for 12 weeks after the end of the treatment period. At week 4, in the middle of the treatment period, subjects received the commercial Canadian influenza vaccine (Vaccine Fluviral® S/F, Shire, Montreal, Canada) containing 15 µg each of A/New Caledonia/20/99, A/Panama/2007/99, B/Victoria/504/2000 antigens

[0053] Influenza-specific proliferative T cell response and antibody titers were evaluated for each of the 3 strains contained in the vaccine. The proliferative T cell response was assessed by a mitogen assay using tritiated thymidine (^{3}H) incorporation and results were log-base 10 transformed prior to analysis. The antibody titers were determined by standard hemaglutination inhibition assay and results were log-base 2 transformed prior to analysis.

[0054] Eighty one (81) subjects completed the study as per protocol. Subject demographics are shown in the following table :

Table 2
Subject demographics

	Placebo	1 mg TH9507	2 mg TH9507	All	P-value
Age (years)	75.9 ± 6.5	74.9 ± 6.1	73.2 ± 4.4	74.6 ± 5.8	0.21
Total N	29	29	29	187	0.96
Female	13	13	14	40	
Male	16	16	15	47	
BMI (kg/m²)	27.4 ± 5.8	26.9 ± 4.2	29.2 ± 6.0	27.8 ± 5.4	0.26

Data for age and BMI are presented as mean ± SD. Baseline comparability among treatment groups was tested by ANOVA (age, BMI) or Pearson's chi-square test (gender).

Results

[0055] As shown in Fig. 3, the mean AUC calculated for the whole study period including both the treatment and follow-up period (week 0 to week 20) was statistically higher in the 2 mg group when compared to placebo (Panama, P=0.03; New Caledonia, P=0.001; Victoria, P=0.02,

(Pairwise comparisons for difference among treatment groups and ANCOVA analysis for overall treatment significance).

[0056] As illustrated in Fig. 4, administration of TH9507 increased the proportion of patients achieving a protective antibody level for the Victoria antigen when compared to placebo. This observation reached statistical significance at the 2 mg dose and was noted during both the treatment and follow-up periods (week 6 : P=0.02; Week 8 : P=0.01; week 12 : P=0.02; week 16 : P=0.004, week 20 : P=0.01, pairwise comparisons for difference among treatment groups and Pearson chi-squared test for overall treatment difference) indicating a sustained effect for up to 16 weeks after cessation of treatment. No statistical difference in the percentage of subjects was observed for the Panama and New Caledonia strains.

[0057] A dose-related increase in the mean IGF-1 values was observed during the whole treatment period in both Th9507 groups when compared to baseline. Values returned to baseline following cessation of treatment.

[0058] No major difference in the incidence of adverse events was observed between treatment groups except for a dose-related trend in the incidence of reactions at the site of injection.

[0059] In summary, the findings observed in this study strongly indicate that TH9507 has a therapeutic potential in immune indications. In particular, its effect on the T-lymphocyte proliferation response following vaccination makes it attractive to develop in clinical situations where the cell-mediated immune system is depressed, such as viral infections in the elderly and immune-deficient states following HIV infection, high-dose chemotherapy or radiotherapy.

Example 3

ThGRF's benefits in wasting/catabolic conditions

[0060] The present example shows the effect of a 7-day administration of TH9507 on circulating IGF-1 levels in healthy middle-aged men.

Material and Methods

[0061] The study used a randomized, double-blind, placebo-controlled design and was conducted in healthy men, aged 50 to 60 years old. Subjects (8 per group) were injected S.C. once a day for 7 consecutive

days with placebo, 0.5, 1 or 2 mg of TH9507. Circulating IGF-1 levels were measured on Days 1 to 7. The 12 hour GH response and TH9507 PK profile were determined on Day 1 and 7.

Results

[0062] As shown in Fig. 5, IGF-1 increased over baseline values by 8% (placebo), 37% (0.5 mg), 89% (1mg) and 106% (2 mg); these increases were statistically significant for all 3 doses of TH9507. The 1 mg and 2 mg doses were equally potent and induced a doubling of IGF-1 levels up to levels expected for young adults (286±25 and 284±55 ng/ml, respectively), none of the subjects exhibited levels greater than 400 ng/ml. A plateau was reached at Day 4 and 6 for the 1 mg and 2 mg doses, respectively.

[0063] GH response to TH9507 increased rapidly both on Days 1 and 2. The increase was dose dependent between the 0.5 and 1 mg dose ($P<0.01$), and was similar at the 1 mg and 2 mg doses. No significant modification in prolactin, ACTH, cortisol, TSH, LH or FSH was observed following single or repeated treatment with TH9507.

[0064] PK analysis indicated that Cmax and AUC parameters increased in function of the dose administered. The half-life of the TH9507 ranged between 2 and 5 hours.

[0065] These results clearly indicate that TH9507 is highly specific on GH secretion and a powerful IGF-1 inducer, suggesting potential clinical benefits in wasting/catabolic conditions.

Example 4

Effects of GRF on non-HDL cholesterol in patients with type 2 Diabetes

[0066] The present example illustrates beneficial effects of TH9507 on non-HDL cholesterol levels in a diabetic population.

Material and Methods

[0067] A double-blind placebo-controlled study was conducted in 53 type II diabetic patients (age = 61 ± 7 [SD]; 34% female) on stable antidiabetic medication (26% on insulin). Patients were randomized to

parallel groups to receive daily subcutaneous administration of a placebo, 1 mg or 2 mg TH9507, respectively.

Results

[0068] A statistically significant difference was observed at Week 12 between the 3 treatment group in the mean total cholesterol change from baseline (P=0.04). Values decreased in the 2 mg group (-11.1 ± 21.9 mg/dl; -6%), as compared to increases in the Placebo (+9.7 ± 22.6 mg/dl; +5%) and 1 mg group (+6.1 ± 16.2 mg/dl; +3%). This effect was accompanied by a decrease in the mean non-HDL cholesterol values in the 2 mg group (-11.5 ± 22.5 mg/dl; -11%) and increases in the placebo (+5.3 ± 17.4 mg/dl; +6%) and 1 mg group (+11.4 ± 20.0 mg/dl; +12%).

[0069] No statistically significant differences were observed between the three groups during the treatment period in terms of insulin relative response to an oral glucose tolerance test. At Week 12, glycosylated hemoglobin (HbA1c) levels displayed a trend for a decrease in the placebo group, a decrease in the 1 mg group, and no change in the 2 mg group. Clinically relevant changes in antidiabetic medications occurred with a similar incidence in the three treatment groups.

[0070] A dose–related increase in IGF-1 levels was observed at the end of the treatment period.

[0071] In summary, this study indicates that the repeated administration of TH9507 for 12 weeks decreases the total and non-HDL cholesterol fraction in diabetic subjects and can be safely administered to this population without impairing glucose control. The effects observed on blood lipids and the known lipolytic properties of GH warrant the investigation of TH9507 for the treatment of syndromes associated with visceral fat accumulation.

[0072] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to

which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A composition improving daytime vigilance and/or cognitive function in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

2. The composition of claim 1, wherein said GRF analog is
X ——GRF Peptide (A)

wherein;

the GRF peptide is a peptide of formula B;

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-Arg-A30-R0 (B)

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

A27 is Met, Ile or Nle;

A28 is Ser or Asn;

A30 is a bond or any amino acid sequence of 1 up to 15 residues;

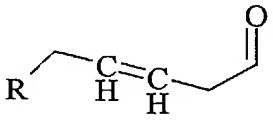
R0 is NH_2 or NH-(CH_2)n-$CONH_2$, with n=1 to 12 and;

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and said hydrophobic tail defining a backbone of 5 to 7 atoms;

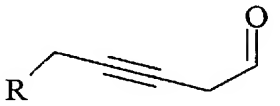
wherein said backbone can be substituted by C1-6 alkyl, C3-6 cycloalkyl, or C6-12 aryl and said backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C3-9 cycloalkyl, and C6-12 aryl.

3. The composition of claim 2, wherein X is selected from the group consisting of:



1 (R=H or CH_3 or CH_2CH_3)
cis or *trans*



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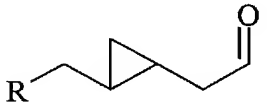
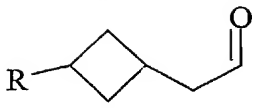


3 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs

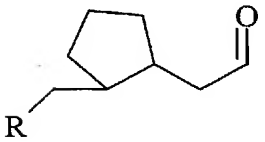
4 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



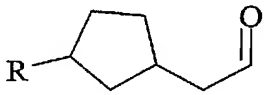
5 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R $\neq$ H)

both as racemic mixtures
or pure enantiomeric pairs



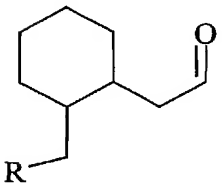
6 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



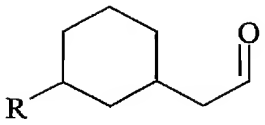
7 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R $\neq$ H)

both as racemic mixtures
or pure enantiomeric pairs



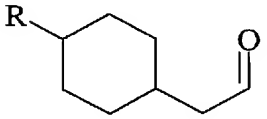
8 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



9 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R ≠ H)

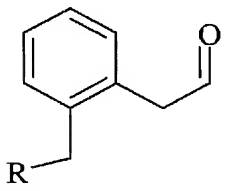
both as racemic mixtures
or pure enantiomeric pairs



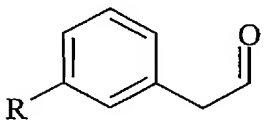
10 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R ≠ H)

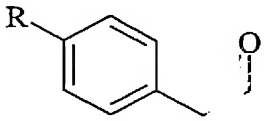
both as racemic mixtures
or pure enantiomeric pairs



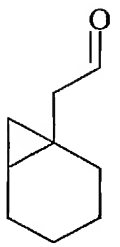
11 (R=H or CH_3 or CH_2CH_3)



12 (R=H or CH_3 or CH_2CH_3)



13 (R=H or CH_3 or CH_2CH_3)



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4. The composition of claim 1, wherein said GRF analog is (hexenoyl trans-3) hGRF(1-44) NH_2.

5. The composition of claim 1, wherein said cognitive function is selected from the group consisting of thinking, reasoning, problem solving and memory.

6. Use of an effective amount of the composition of any one of claims 1 to 5 for improving daytime vigilance and/or cognitive function in a subject.

7. The use as claimed in claim 6, wherein said composition is administered in an amount of about 0,0001 to 1 mg/kg per day to said subject.

8. The use as claimed in claim 6, wherein said composition is administered from a route selected from the group consisting of oral, transdermal, intravenous, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical route.

9. A method for improving daytime vigilance and/or cognitive function in a subject, the method comprising the step of administering an effective amount of the composition of any one of claims 1 to 5 to said subject.

10. The method of claim 9, wherein said composition is administered in an amount of about 0,0001 to 1 mg/kg per day to said subject.

11. The method of claim 9, wherein said composition is administered from a route selected from the group consisting of oral, transdermal, intravenous, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical route.

12. A composition for improving a metabolic condition in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

13. The composition of claim 22, wherein said GRF analog is

X ——GRF Peptide (A)

wherein;

the GRF peptide is a peptide of formula B;

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-Arg-A30-R0 (B)

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

A27 is Met, Ile or Nle;

A28 is Ser or Asn;

A30 is a bond or any amino acid sequence of 1 up to 15 residues;

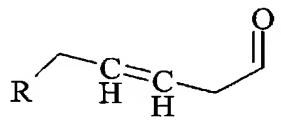
R0 is NH_2 or NH-(CH_2)n-$CONH_2$, with n=1 to 12 and;

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and said hydrophobic tail defining a backbone of 5 to 7 atoms;

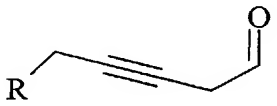
wherein said backbone can be substituted by C1-6 alkyl, C3-6 cycloalkyl, or C6-12 aryl and said backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C3-9 cycloalkyl, and C6-12 aryl.

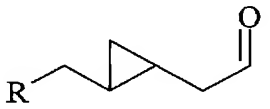
14. The composition of claim 13, wherein X is selected from the group consisting of:



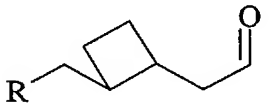
1 (R=H or CH_3 or CH_2CH_3)
cis or *trans*



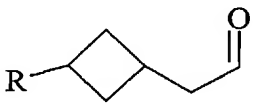
2 (R=H or CH_3 or CH_2CH_3)



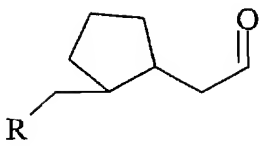
3 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



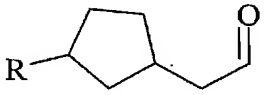
4 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



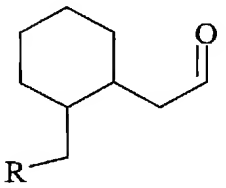
5 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



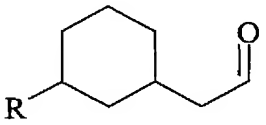
6 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



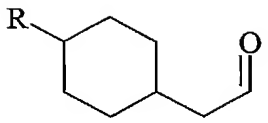
7 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



8 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



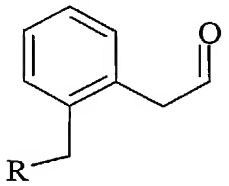
9 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



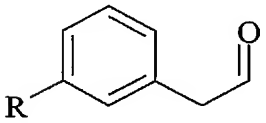
10 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R ≠ H)

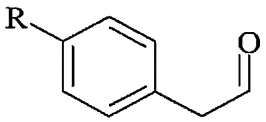
both as racemic mixtures
or pure enantiomeric pairs



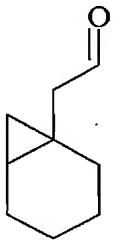
11 (R=H or CH_3 or CH_2CH_3)



12 (R=H or CH_3 or CH_2CH_3)



13 (R=H or CH_3 or CH_2CH_3)



14

15. The composition of claim 12, wherein said GRF analog is (hexenoyl trans-3) hGRF(1-44)NH_2.

16. The composition of claim 12, wherein said metabolic condition is associated with fat accumulation and/or hypercholesterolemia.

17. The composition of claim 12, wherein said metabolic condition is selected from the group consisting of obesity, HIV-related lipodystrophy, metabolic syndrome and syndrome X.

18. Use of an effective amount of the composition of any one of claims 12 to 17 for improving a metabolic condition in a subject.

19. The use as claimed in claim 18, wherein said composition is administered in an amount of about 0,001 to 1 mg/kg per day to said subject.

20. The use as claimed in claim 19, wherein said composition is administered from a route selected from the group consisting of oral, transdermal, intravenous, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, patenteral, intrarectal and topical route.

21. A method for improving a metabolic condition in a subject, the method comprising the step of administering an effective amount of the composition of any one of claims 12 to 17 to said subject.

22. The method of claim 21, wherein said composition is administered in an amount of about 0,0001 to 1 mg/kg per day to said subject.

23. The method of claim 22, wherein said composition is administered from a route selected from the group consisting of oral, transdermal, intravenous, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical route.

24. A composition for improving anabolism in a catabolic condition in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

25. The composition of claim 24, wherein said GRF analog is

X ——GRF Peptide (A)

wherein;

the GRF peptide is a peptide of formula B;

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-Arg-A30-R0 (B)

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

A27 is Met, Ile or Nle;

A28 is Ser or Asn;

A30 is a bond or any amino acid sequence of 1 up to 15 residues;

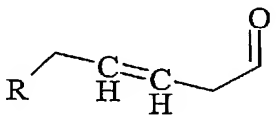
R0 is NH_2 or NH-(CH_2)n-$CONH_2$, with n=1 to 12 and;

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and said hydrophobic tail defining a backbone of 5 to 7 atoms;

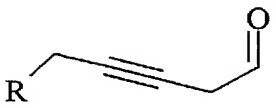
wherein said backbone can be substituted by C1-6 alkyl, C3-6 cycloalkyl, or C6-12 aryl and said backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C3-9 cycloalkyl, and C6-12 aryl.

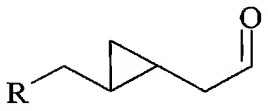
26. The composition of claim 25, wherein X is selected from the group consisting of:



1 (R=H or CH_3 or CH_2CH_3)
cis or *trans*

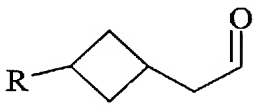


2 (R=H or CH_3 or CH_2CH_3)

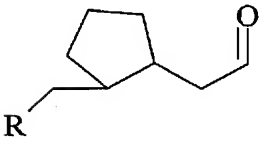


3 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs

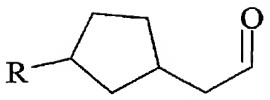
4 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



5 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



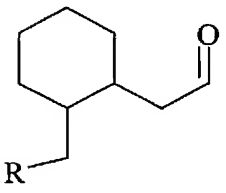
6 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



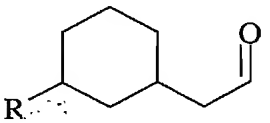
7 (R=H or CH_3 or CH_2CH_3)

cis or *trans,* (when R ≠ H)

both as racemic mixtures
or pure enantiomeric pairs



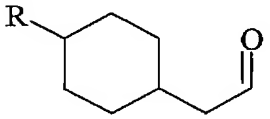
8 (R=H or CH_3 or CH_2CH_3)
cis or *trans,* both as racemic mixtures
or pure enantiomeric pairs



9 (R=H or CH_3 or CH_2CH_3)

cis or *trans,* (when R ≠ H)

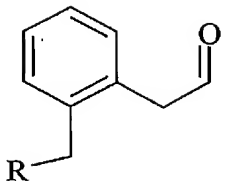
both as racemic mixtures
or pure enantiomeric pairs



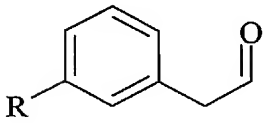
10 (R=H or CH_3 or CH_2CH_3)

cis or *trans,* (when R ≠ H)

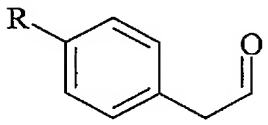
both as racemic mixtures
or pure enantiomeric pairs



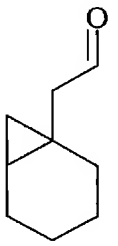
11 (R=H or CH_3 or CH_2CH_3)



12 (R=H or CH_3 or CH_2CH_3)



13 (R=H or CH_3 or CH_2CH_3)



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27: The composition of claim 24, wherein said GRF analog is (hexenoyl trans-3) hGRF(1-44)NH_2.

28. The composition of claim 24, wherein said catabolic condition is muscular wasting.

29. The composition of claim 24, wherein the catabolic condition is related to one selected from the group consisting of chronic renal failure, congestive heart failure, AIDS, hip fracture, trauma or major surgery in a subject.

30. The composition of claim 29, wherein said subject is an elderly subject.

31. Use of an effective amount of the composition of any one of claims 24 to 30 for improving anabolism in a catabolic condition in a subject.

32. The use as claimed in claim 31, wherein said composition is administered in an amount of about 0,0001 to 1 mg/kg per day to said subject.

33. The use as claimed in claim 31, wherein said composition is administered from a route selected from the group consisting of oral, transdermal, intravenous, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical route.

34. A method for improving anabolism in a catabolic condition in a subject, the method comprising the step of administering an effective amount of the composition of any one of claims 24 to 30 to said subject.

35. The method of claim 34, wherein said composition is administered in an amount of about 0,0001 to 1 mg/kg per day to said subject.

36. The method of claim 34, wherein said composition is administered from a route selected from the group consisting of oral, transdermal, intravenous, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical route.

37. A composition for improving and/or reconstituting immune function in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

38. The composition of claim 37, wherein said GRF analog is

X ——GRF Peptide (A)

wherein;

the GRF peptide is a peptide of formula B;

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-Arg-A30-R0 (B)

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

A27 is Met, Ile or Nle;

A28 is Ser or Asn;

A30 is a bond or any amino acid sequence of 1 up to 15 residues;

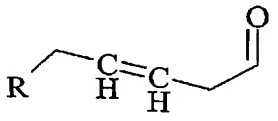
R0 is NH_2 or NH-(CH_2)n-$CONH_2$, with n=1 to 12 and;

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and said hydrophobic tail defining a backbone of 5 to 7 atoms;

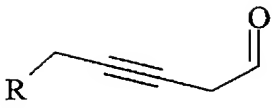
wherein said backbone can be substituted by C1-6 alkyl, C3-6 cycloalkyl, or C6-12 aryl and said backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C3-9 cycloalkyl, and C6-12 aryl.

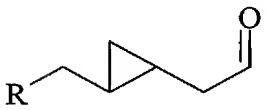
39. The composition of claim 38, wherein X is selected from the group consisting of:



1 (R=H or CH_3 or CH_2CH_3)
cis or *trans*



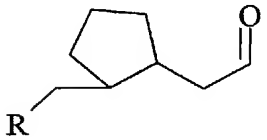
2 (R=H or CH_3 or CH_2CH_3)



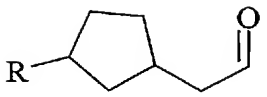
3 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs

4 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs

5 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, (when R $\neq$ H)
both as racemic mixtures
or pure enantiomeric pairs



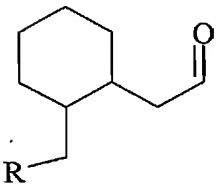
6 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



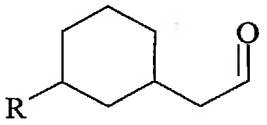
7 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R ≠ H)

both as racemic mixtures
or pure enantiomeric pairs



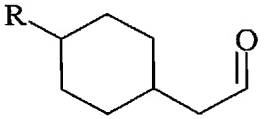
8 (R=H or CH_3 or CH_2CH_3)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



9 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R ≠ H)

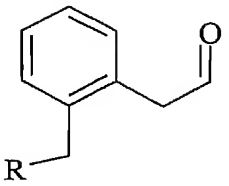
both as racemic mixtures
or pure enantiomeric pairs



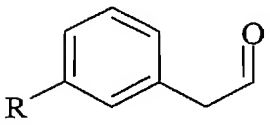
10 (R=H or CH_3 or CH_2CH_3)

cis or *trans*, (when R ≠ H)

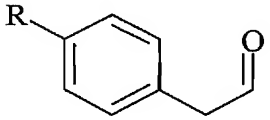
both as racemic mixtures
or pure enantiomeric pairs



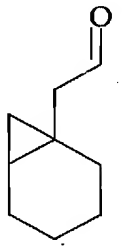
11 (R=H or CH_3 or CH_2CH_3)



12 (R=H or CH_3 or CH_2CH_3)



13 (R=H or CH_3 or CH_2CH_3)



14

40. The composition of claim 37, wherein said GRF analog is (hexenoyl trans-3) hGRF(1-44)NH_2.

41. The composition of claim 37, wherein said subject is in an immune deficiency state.

42. The composition of claim 41, wherein said immune deficiency state is caused by one selected from the group consisting of aging, HIV infection, chemotherapy treatment and radiotherapy treatment.

43. Use of an effective amount of the composition of any one of claims 37 to 42 for improving and/or reconstituting immune function in a subject.

44. The use as claimed in claim 43, wherein said composition is administered in an amount of about 0,0001 to 1 mg/kg per day to said subject.

45. The use as claimed in claim 43, wherein said composition is administered by a route selected from the group consisting of oral, transdermal, intravenous, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical route.

46. A method for improving and/or reconstituting immune function in a subject, the method comprising the step of administering an effective amount of the composition of any one of claims 37 to 42 to said subject.

47. The method of claim 46, wherein said composition is administered in an amount of about 0,0001 to 1 mg/kg per day to said subject.

48. The method of claim 46, wherein said composition is administered from a route selected from the group consisting of oral, transdermal, intravenous, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical route.

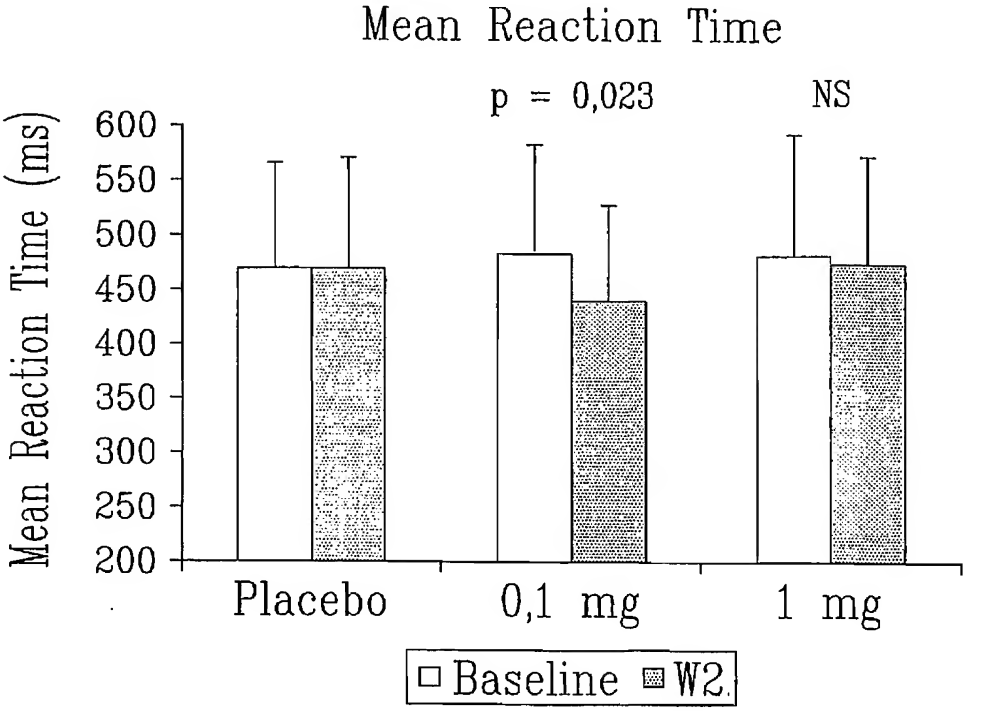


Fig. 1

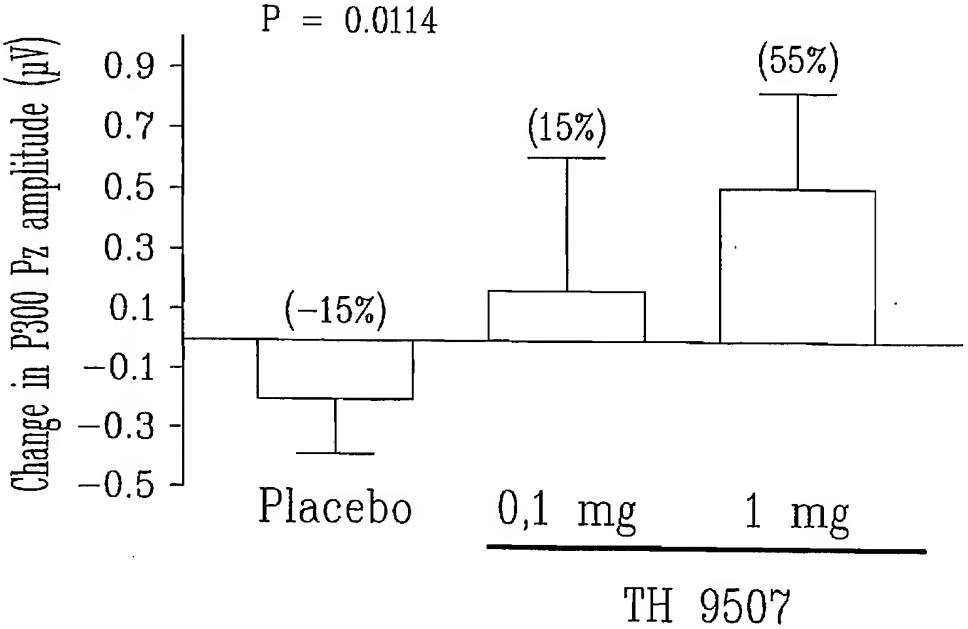


Fig. 2

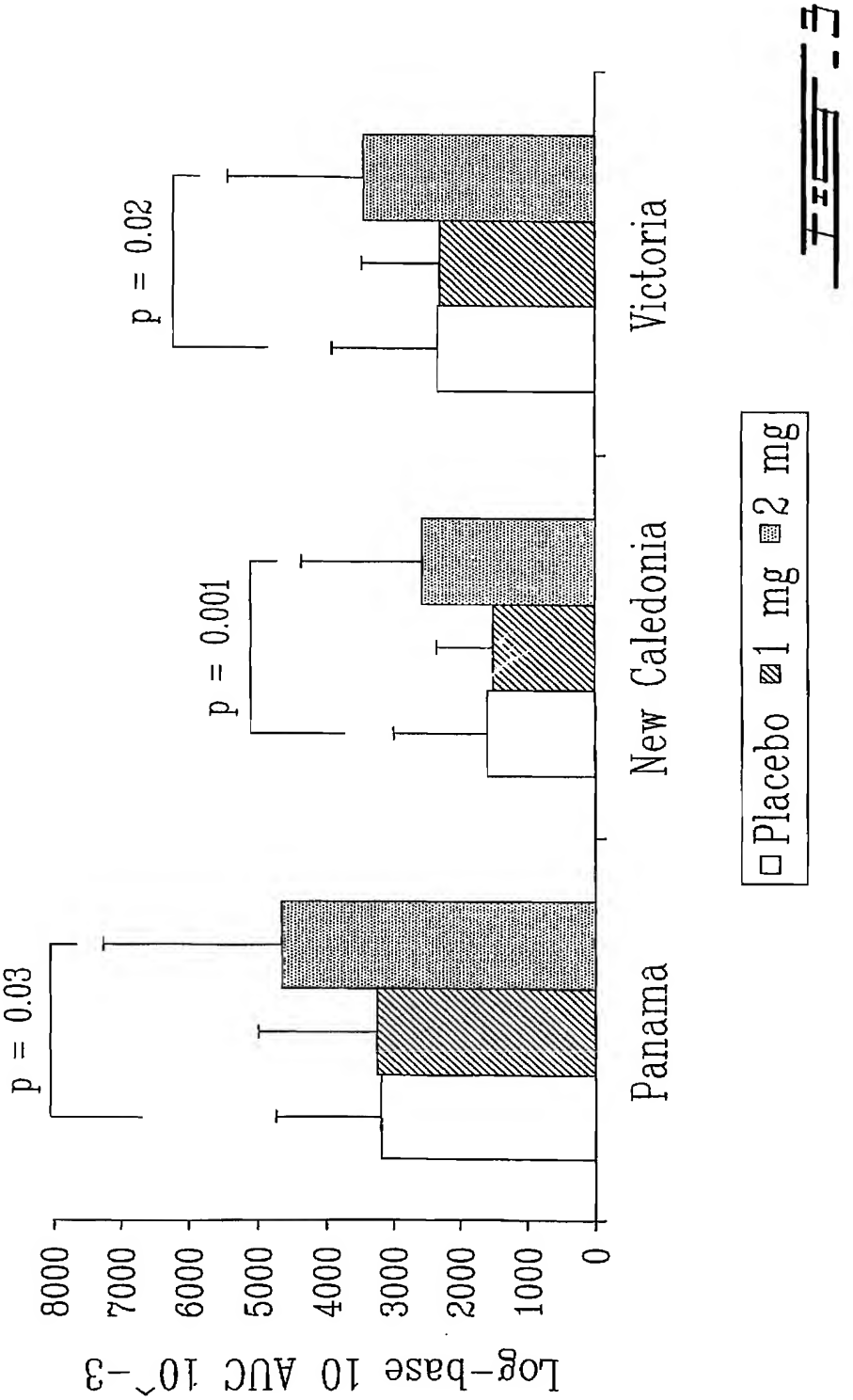


Fig. 3

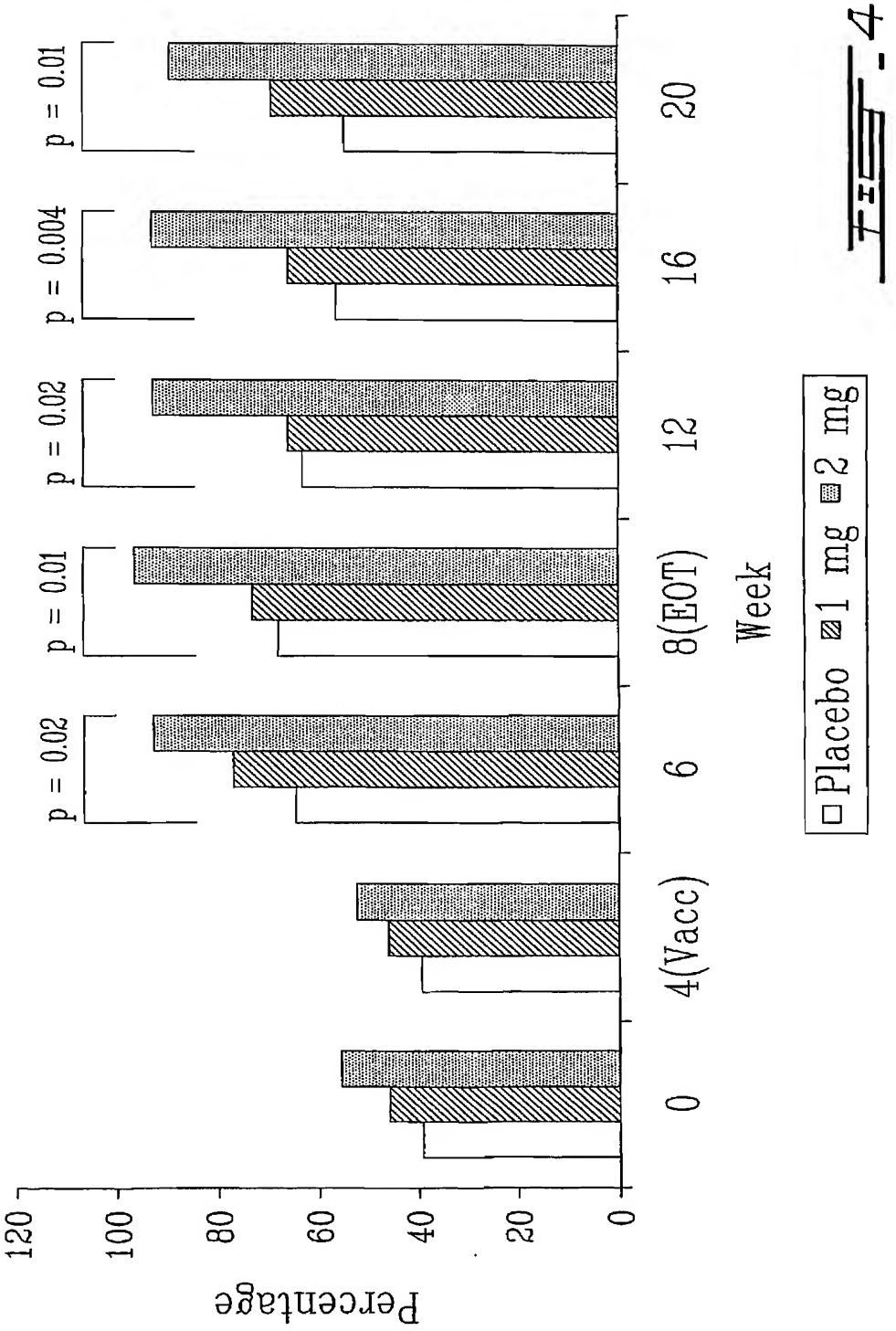


Fig-4

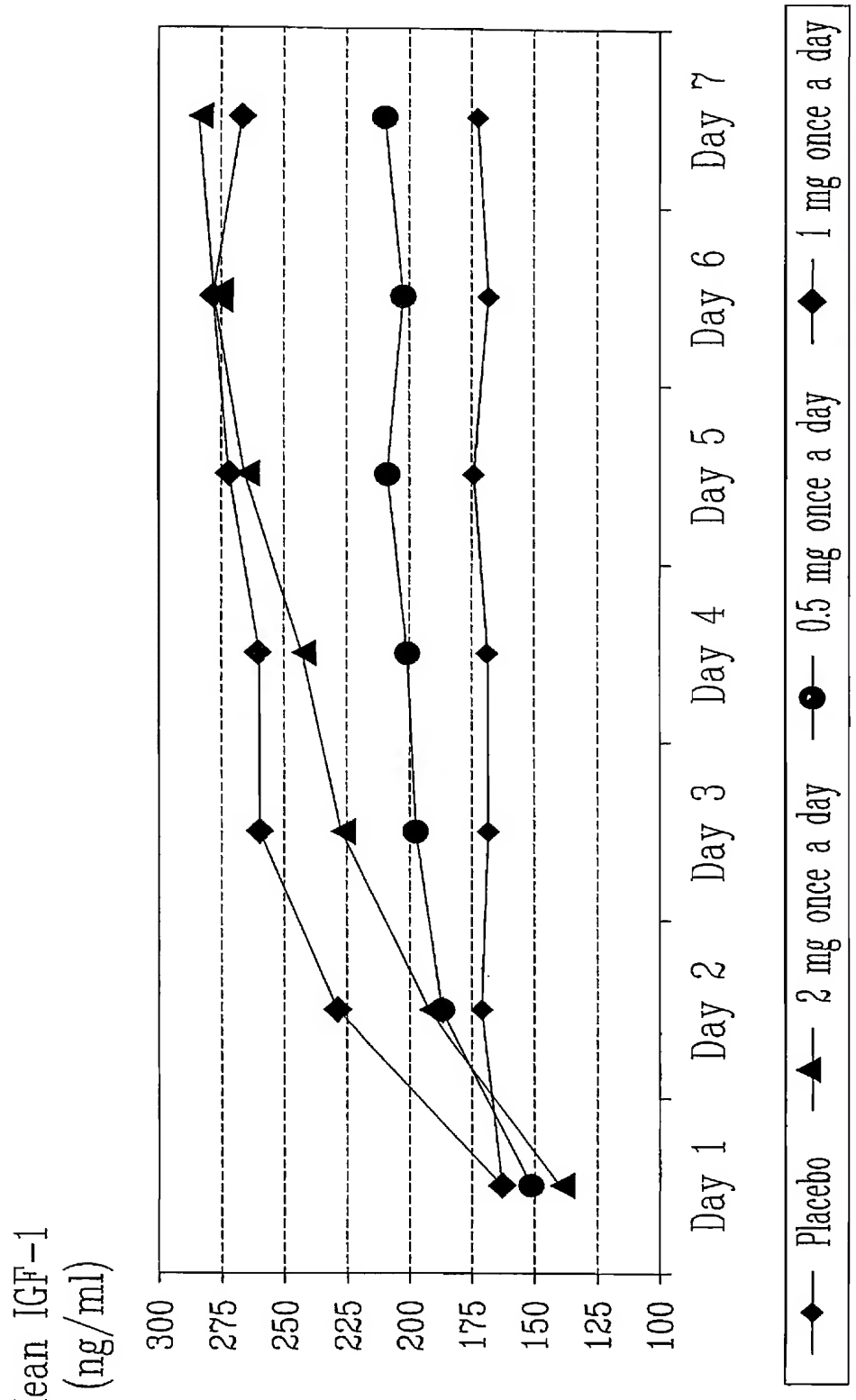


FIG. 5

SEQUENCE LISTING

<110> Theratechnologies Inc.
Abribat, Thierry
De Villers, André
Allas, Soraya
Gravel, Denis
Chapdelaine, Alcide

<120> New indications for GRF analogs

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/00827

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/25 A61P25/28 A61P3/00 A61P21/06 A61P37/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/14236 A (THERATECHNOLOGIES INC ;BRAZEAU PAUL (CA); GRAVEL DENIS (CA); HABI) 16 March 2000 (2000-03-16)	1-5, 12-42
Y	page 7, line 1 -page 8, line 3; claims; figures 7A,7B; example XI page 13, line 19 - line 26	6-11
Y	P.L. THORNTON ET AL.: "Chronic 'D-Ala2!GHRH administration increases working memory in aged rats." ABSTRACTS OF THE SOCIETY FOR NEUROSCIENCE., vol. 23, no. 1, 1997, page 532 XP002267995 SOCIETY FOR NEUROSCIENCE, WASHINGTON, DC., US ISSN: 0190-5295 abstract 208.7	6-11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2004	-8. 06. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ryckebosch, A

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/00827

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1990 X.A. ALVAREZ ET AL.: "EFFECTS OF GRF 1-29 AMIDE NH-2 ON SHORT-TERM MEMORY NEUROENDOCRINE AND NEUROPSYCHOLOGICAL ASSESSMENT IN HEALTHY YOUNG SUBJECTS" Database accession no. PREV199191065562 XP002267998 abstract & METHODS AND FINDINGS IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY, vol. 12, no. 7, 1990, pages 493-500, ISSN: 0379-0355 ---	6-11
Y	S. SCHNEIDER-RIVAS ET AL.: "Modulation of long-term memory and extinction responses induced by growth hormone (GH) and growth hormone releasing hormone (GHRH) in rats." LIFE SCIENCES, vol. 56, no. 22, 1995, pages PL 433-PL 441, XP002267996 the whole document ---	6-11
Y	A. ALEMAN ET AL.: "Insulin-like growth factor-I and cognitive function in healthy older men." JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 84, no. 2, 1999, pages 471-475, XP002267997 cited in the application page 474, right-hand column, paragraph 3 - last line ---	6-11
X	THERATECHNOLOGIES INC.: "ThGRF in HIV-related lipodystrophy: Phase II clinical trial in Canada and the US." , 'Online! 22 May 2003 (2003-05-22), XP002280165 Retrieved from the Internet: <URL:http://www.medibolics.com/NewLipodystrophyDrug.htm> 'retrieved on 2004-05-13! the whole document --- -/--	1-48

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT/CA 03/00827

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THERATECHNOLOGIES PRESS RELEASES: "Theratechnologies clinically demonstrates improvement in immune function among elderly with ThGRF peptide." , 'Online! 6 June 2002 (2002-06-06), pages 1-3, XP002280166 Retrieved from the Internet: <URL:http://www.theratech.com/english/press/2002/0606-2002.htm> 'retrieved on 2004-05-13! the whole document	1-48

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/00827

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-11, 18-23, 31-36 and 43-48 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-48 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-11

   Composition and method for improving daytime vigilance and/or cognitive function in a subject, comprising administering a GRF compound or an analog thereof.

2. Claims: 12-23

   Composition and method for improving a metabolic condition in a subject, comprising administering a GRF compound or an analog thereof.

3. Claims: 24-36

   Composition and method for improving anabolism in a catabolic condition in a subject, comprising administering a GRF compound or an analog thereof.

4. Claims: 37-48

   Composition and method for improving and/or reconstituting immune function in a subject, comprising administering a GRF compound or analog thereof.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-48 (all in part)

Present claims 1-48 (all in part) relate to a composition/use comprising a compound defined by reference to a desirable characteristic or property, namely analogs of a GRF compound.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds GRF, as defined in claim 1, and the GRF analog as defined on page 9, paragraph '0031! and the examples of the description, i.e. 'hexenoyl-trans-3-Tyr1!hGRF(1-44)NH2, identified as TH 9507.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

tion on patent family members

International Application No
PCT/CA 03/00827

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0014236 A	16-03-2000	US 6020311 A	01-02-2000
		US 6458764 B1	01-10-2002
		AU 755852 B2	19-12-2002
		AU 5500799 A	27-03-2000
		BR 9913515 A	05-06-2001
		CA 2342070 A1	16-03-2000
		WO 0014236 A2	16-03-2000
		DE 1109909 T1	23-05-2002
		EP 1109909 A2	27-06-2001
		ES 2164626 T1	01-03-2002
		JP 2002524472 T	06-08-2002

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(19) World Intellectual Property Organization
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9 December 2004 (09.12.2004)

PCT

(10) International Publication Number
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(21) International Application Number: PCT/CA2003/000827

(22) International Filing Date: 29 May 2003 (29.05.2003)

(25) Filing Language: English

(26) Publication Language: English

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(72) Inventors; and

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(74) Agents: **SHAHINIAN, Serge, S.** et al.; Goudreau Gage Dubuc, Stock Exchange Tower, 800 Place Victoria, Suite 3400, P.O. Box 242, Montréal, Québec H4Z 1E9 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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(48) Date of publication of this corrected version:
22 December 2005

(15) Information about Correction:
see PCT Gazette No. 51/2005 of 22 December 2005, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GRF ANALOG COMPOSITIONS AND THEIR USE

(57) Abstract: The present invention relates to compositions for improving daytime vigilance and/or cognitive function, for improving a metabolic condition, for improving anabolism in a catabolic condition and for improving and/or reconstituting immune function in a subject, the composition comprising an effective amount of a GRF compound or analog thereof in association with a pharmaceutically acceptable carrier, excipient or diluent.

WO 2004/105789 A1